UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ARNE HOLMGREN, MARJAN H. AMIRI and HIROYUKI MASAYASU

Appeal No. 2005-0936
Application No. 09/926,218

ON BRIEF

Before ELLIS, SCHEINER and ADAMS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 13-25, the only claims remaining in the application. Claims 13-25 are reproduced in the Appendix accompanying appellants' Brief on Appeal of August 24, 2004.

The references relied on by the examiner are:

Müller et al. (Müller), "A Novel Biologically Active Seleno-Organic Compound – Glutathione Peroxidase-Like Activity *In Vitro* and Antioxidant Capacity of PZ 51 (Ebselen)," Biochemical Pharmacology, Vol. 33, No. 20, pp. 3235-3239 (1984)

Arteel et al. (Arteel), "Function of Thioredoxin Reductase as a Peroxynitrite Reductase Using Selenocystine or Ebselen," Chem. Res. Toxicol., Vol. 12, pp. 264-269 (1999).

Claims 13-25 stand rejected under 35 U.S.C. § 102 (b) as anticipated by Arteel. In addition, claims 13-25 stand rejected under 35 U.S.C. § 103 as unpatentable over Arteel and Müller.

We reverse these rejections, and raise an additional issue for consideration.

BACKGROUND

The thioredoxin/thioredoxin reductase system regulates reversible reduction-oxidation of thiol groups and maintains a constant thiol level in vivo to prevent functional depression of thiol proteins by formation of disulfide bonds and advanced peroxidation. Thioredoxin reductase reductively cleaves a disulfide bond on a target protein in the presence of NADPH and thioredoxin. Thioredoxin is a protein containing two thiol groups, and also functions as a proton donor in reduction of ribonucleotide by ribonucleotide reductase. Specification, page 1.

According to appellants, selenium compounds such as 2-phenyl-1,2-benzisoselenazol-3(2H)-one (hereinafter, ebselen) "can function as [substrates] of thioredoxin reductase by repeated self reduction-oxidation similarly to thioredoxin in the thioredoxin/thioredoxin reductase system," and can "enhance peroxidase activity of thioredoxin reductase in the presence of thioredoxin reductase and thioredoxin" (id., pages 1-2). Appellants further explain that selenium compounds were known to reduce peroxides "by [a] glutathione-like activity . . . [but], the reduction of a peroxide by glutathione peroxidase is based on [a] totally different mechanism . . . [than that of] thioredoxin reductase" (id., page 2).

DISCUSSION

The present invention is directed to a method of reducing a substrate with thioredoxin reductase (claims 13 and 14); a method of enhancing the peroxidase activity of thioredoxin reductase in the presence of NADPH, thioredoxin and a substrate (claims 15, 16, 20 and 21); a method of oxidzing reduced thioredoxin by a substrate (claim 17); a method for reducing a peroxide by combining thioredoxin, thioredoxin reductase, NADPH and a substrate (claims 18, 22 and 23); and finally, a method of

preventing peroxidation of a substance by combining the substance with thioredoxin, thioredoxin reductase, NADPH and a substrate (claims 19, 24 and 25). Claims 20-25 require that these reactions occur in vivo. The substrate in all of these claims is a selenium compound, and for purposes of this appeal, we will focus on a particular selenium compound, ebselen. The common thread that runs through all of these claims is the cyclical reduction and re-oxidation of the substrate (in this case, ebselen) in the presence of thioredoxin reductase and NADPH; i.e., ebselen is repeatedly reduced to ebselen selenol, and re-oxidized to ebselen.

The examiner rejected all of the claims under 35 U.S.C. § 102 (b) as anticipated by Arteel. In view of its brevity, we reproduce the examiner's rejection in its entirety (Answer, pages 3-4):

> Arteel is teaching a substrate for thioredoxin reductase which has the same formula as claimed herein, see the title, wherein Ebselen is mentioned. This is the same as the 2-phenyl-1,2-benzisoselen[a]zol-3(2H). See line 1 of the abstract, wherein mammal is cited, column 1, 2nd paragraph, lines 1-3 and 7-8, column 2, 1st paragraph on page 264, teach all the elements of the instant claims.

Arteel describes the activity of mammalian thioredoxin reductase as a peroxynitrite reductase. Appellants concede that Arteel performs experiments with thioredoxin reductase and ebselen, but argue essentially that under the conditions used in the reference, i.e., in the presence of both ebselen and peroxynitrite, "[t]he strong oxidant peroxynitrite is reduced by thioredoxin reductase . . . and ebselen is oxidized to ebselen selenoxide which is reduced by thiodoxin reductase" (Brief, page 14). Appellants emphasize that the substrates of the present claims "do not include ebselen selenoxide" (id., page 13).

In contrast to Arteel's system, according to appellants, "the reaction of ebselen in [a]ppellant's system does not form ebselen selnoxide" (id.); instead, "ebselen is a substrate being reduced by NADPH and thioredoxin reductase . . . [and] undergo[es] unlimited cycles of oxidation/reduction in the presence of hydrogen peroxide without affecting the activity of the enzyme. The reduced ebselen is called ebselen selenol and . . . is oxidized back to ebselen by hydrogen peroxide . . . and a new cycle starts . . . driven by NADPH" (id., page 16).

Finally, appellants point out that none of Arteel's reactions occurs in vivo, as required by claims 20-25.

The examiner's response to these arguments is to assert, for the first time, and without further explanation, that Arteel's "Figure 6[ ] is the same method as claimed by [ ] appellants" (Answer, page 6); and that page 267, column 1, last paragraph, . . . expressly [teaches] that ebselen is [a] substrate" (id.). On cursory inspection, these excerpts of Arteel appear to concern reduction of a diselenide (ebselen is not a diselenide) on the one hand, and reduction of ebselen selenoxide (with the reaction cycling between ebselen and ebselen selenoxide, rather than cycling between ebselen and ebselen selenol, as required by the present claims) on the other.

With respect claims 20-25, directed to in vivo methods, we agree with appellants that the mere description of thioredoxin reductase as a mammalian enzyme is not a description of an in vivo reaction involving ebselen.

"[E]very limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997). Moreover, "the Patent Office has the initial burden of

coming forward with some sort of evidence tending to disprove novelty." In re Wilder, 429 F.2d 447, 450, 166 USPQ2d 545, 548 (CCPA 1970). We find that the examiner's initial burden of establishing a prima facie case of anticipation has not been met. The rejection of claims 13-25 under 35 U.S.C. § 102 (b) as anticipated by Arteel is reversed.

Obviousness

The examiner also rejected claims 13-25 under 35 U.S.C. § 103 as unpatentable over the combined teachings of Arteel and Müller. According to the examiner, Arteel does not teach that ebselen "is also an enhancer of the peroxidase activity of thioredoxin reductase" (Answer, page 4), and cites Müller as teaching that ebselen is known to be an enhancer of peroxidase activity.

Nevertheless, Müller concerns the glutathione peroxidase-like activity of ebselen, and the examiner has not begun to explain how this would be relevant to the claimed invention, especially in light of the present specification's teaching that "the reduction of a peroxide by glutathione peroxidase is based on [a] totally different mechanism . . . [than that of] thioredoxin reductase" (Specification, page 2). The examiner's reliance on Müller does nothing to resolve the underlying deficiencies of Arteel's disclosure.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The rejection under 35 U.S.C. § 103 is reversed because the examiner has not established that the subject matter of claims 13-25 would have been suggested by the prior art.

AN ADDITIONAL ISSUE

It appears from the record that ebselen has been known in the art for some time as an anti-oxidant, and may have been administered in vivo prior to the effective filing date of the present application. It is not clear from the record whether appellants and the examiner have determined whether or not this is the case, and if so, whether administration of ebselen in vivo inherently results in the activities required by the claims.

CONCLUSION

On consideration of the record, the rejections of the claims under 35 U.S.C. §§ 102 (b) and 103 are reversed.

REVERSED

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